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AIDS Treatment News

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Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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This proposal, now introduced in Congress as HR 417, would replace current drug marketing with system better designed to reward effective innovation. All drugs would be treated as generics immediately when approved by the FDA, and patent holders would be rewarded from a $60 billion a year award fund for innovations that actually led to better health.

Medical Innovation and Patent Gridlock.....

Is today's sheer multitude of biological patents (especially on genetics of human beings or human pathogens) killing medical innovation -- in addition to generating prohibitive prices for vital medical care?

Tipranavir (Aptivus): Approval Cautiously Recommended

by John S. James

Tipranavir (brand name Aptivus), a protease inhibitor that usually works against HIV that is resistant to other protease inhibitors, was recommended for approval by the FDA's Antiviral Drugs Advisory Committee at a meeting on May 19, 2005. The drug, manufactured by Boehringer Ingelheim, is widely expected to be approved in June 2005.

The advisory committee recommended approval by a vote of 11-3, because of the great need for the drug, and its demonstrated efficacy (greater percentage of patients achieving a treatment response, defined for this study as at least a one log [10 fold] viral load reduction) compared with a non-tipranavir regimen, for multiple-PI resistant volunteers. But the entire committee was cautious about

tipranavir, mainly because of safety "signals" -- indications that there might be problems when the drug is widely used for longer times and with less physician expertise and monitoring than in the clinical trials or expanded-access program. Also, drug interactions with tipranavir can be unusually complex, making correct dosing of both tipranavir, and certain other drugs used at the same time, more difficult.

Physicians and interested patients will benefit from following the recommendations and practices of leading HIV physicians regarding tipranavir. Current information will be free and accessible to anyone at Web sites such as http://www.clinicaloptions.com/hiv, http://www.thebodypro.com, http://www.medscape.com/hiv-aidshome, and http://www.aidsmeds.com (aidsmeds.com is primarily for patients; the other three are written mainly for medical professionals).

The recommendation for approval was based on 24 weeks of data in two clinical trials, called RESIST-1 and RESIST-2. These trials together tested tipranavir in well over 1,000 patients who had taken a median of 12 antiretroviral drugs and were heavily resistant (97% tested resistant to at least one protease inhibitor). These volunteers had a background regimen of approved drugs (NRTIs, NNRTIs, and/or Fuzeon [enfuvirtide, also known as T-20]) designed for them based on genotypic resistance tests, and then were randomized to receive with it boosted tipranavir or with a comparator boosted protease inhibitor. Note that based on genotypic resistance testing, 87% of the volunteers were possibly or definitely resistant to the comparison protease inhibitor. The main goal of these trials was to see if tipranavir combined with the usually inadequate background regimen helped more patients achieve at least a one-log drop in viral load. More than twice the percentage of patients achieved this drop in the tipranavir arm than in the comparison protease inhibitor arm, so tipranavir was deemed to have proven efficacy.

When considering tipranavir, here are some aspects to keep in mind (at least for the near future). Always check for recent information, because it will change due to new results from clinical trials, and new physician experience.

1. Combination with Fuzeon (enfuvirtide): Tipranavir worked much better in reducing HIV viral load in highly treatment experienced patients when combined with Fuzeon. Probably this happened not because of anything special about Fuzeon, but because HIV treatment works best when at least two drugs in a regimen are highly active against the patient's virus -- and the volunteers in the two large phase III tipranavir trials from which most data are available (the trials are named RESIST 1 and RESIST 2) already had substantial resistance to almost all antiretrovirals available. But they had much less resistance to tipranavir because of its different resistance pattern. They also had little or no enfuvirtide resistance because this drug is in a different class -- fusion inhibitors -- from all other approved antiretrovirals (so there is no cross resistance), and 88% of these volunteers had no prior exposure to enfuvirtide itself.

Fuzeon is very expensive, and inconvenient to use because it is injected twice a day. When "small molecule" fusion inhibitors are available -- or drugs in new classes, with different mechanisms of action -- patients largely resistant to currently available antiretrovirals will have alternative choices.

2. Liver toxicity: In the RESIST 1 and 2 trials together, 10% of volunteers taking tipranavir developed new grade 3 or 4 ALT or AST elevations (compared to 3% taking a comparison boosted protease inhibitor). Very few of these volunteers had clinical symptoms of liver problems (as opposed to blood-test results) so far, after at least 24 weeks of tipranavir use. But experts are concerned, because they cannot rule out the possibility that, if patients are left with such high ALT or AST values for long

periods, permanent damage might be done before symptoms develop. Monitoring will be recommended, although it is not clear what will happen if these patients have no satisfactory alternative to using tipranavir.

More studies will be necessary to determine the safety of tipranavir in patients with hepatitis B or C co-infection.

3. Cholesterol and triglyceride elevations: In the RESIST 1 and 2 trials, more volunteers taking tipranavir developed grade 3 or 4 cholesterol or triglycerides than did volunteers in the comparison arm without tipranavir.

4. Skin reactions, especially in women: In a phase I study, 53% of healthy, HIV-negative women developed a skin rash while taking tipranavir combined with an oral contraceptive. In the RESIST trials, 8.5% of HIV-positive women compared with 6.54% of HIV-positive men experienced a rash. No grade 3 or 4 rashes have been reported.

Could tipranavir be like nevirapine (another antiretroviral, coincidentally made by the same company) in that it causes a potentially serious rash that is more common in women than in men -- and more common in people with a high CD4 count than in those with more advanced HIV disease (probably because this particular kind of rash depends on immune functions that are partly suppressed by HIV)? No one knows, because not enough women or people with high CD4 counts have taken tipranavir in clinical trials (where the data is collected and recorded most thoroughly than in medical practice). Boehringer Ingelheim has fully enrolled a trial of tipranavir for treatment-naive volunteers, but since only about 20% of them are women, and this trial enrolled people with advanced HIV disease, it is unlikely to give definitive answers about who is most likely to get the rash.

5. Drug interactions: We noted above that these can be complex and difficult when tipranavir is combined (either with HIV treatments or with other drugs). And the thinking at this time is that tipranavir is NOT suitable for the double-boosted protease inhibitor strategy. Here as elsewhere it will be important to watch what expert consensus develops regarding tipranavir.

Note: *AIDS Treatment News* did not attend the Advisory Committee hearing because of a schedule conflict. The above summary is mostly from a 43-page briefing paper prepared by FDA staff for the Antiviral Drugs Advisory Committee (dated April 22, 2005 and available at
www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4139b1-01-fda.pdf
and from activist reports from the meeting.

What is known about tipranavir will change rapidly, over the next few months especially. Be sure to check publication dates, and use current information.

ADAP Status Now: What You Can Do

by Suzy Subways

Each month, almost 700 low-income Americans living with HIV apply to become clients of the AIDS Drug Assistance Program (ADAP), which pays for anti-HIV medications to treat those without health insurance (or without adequate coverage). Unlike with Medicaid and Medicare, ADAP does not require that a person be disabled by AIDS in order to be eligible -- meaning that treatment can be provided early enough to prevent disability and serious illness. However, consistent under-funding by the federal government has led states to limit access to the program in an effort to balance their budgets.

On June 8, the National Alliance of State and Territorial AIDS Directors (NASTAD) announced that almost 2,000 people living with HIV are on ADAP waiting lists in 10 states. Although most of these are now receiving medications through a special patient assistance program announced by President Bush in June 2004, that program is set to expire this September. No funding has been allocated to continue it, so states expect that these individuals will have to get back in line for ADAP -- at the risk of

treatment interruptions that could lead to HIV drug resistance. The remaining 453 people on waiting lists in eight states are not covered by the President's Initiative.

Eleven states have capped enrollment (which means anyone new will be put on a waiting list) or other restrictions, such as: Fuzeon waiting lists; no coverage for HIV/hepatitis C co-infection treatment; requiring clients to make co-payments and/or re-apply to the program every six months; and narrower definitions of who is eligible for the program. In April, the National ADAP Working Group announced that an additional $303 million will be needed to cover ADAP's new clients in fiscal year 2006 -- and $150 million of that is needed right now. President Bush has proposed a scanty $10 million increase for ADAP in fiscal year 2006 -- only about 3 percent of what will be needed next year.

Activist efforts, mainly coordinated by the Save ADAP committee of the AIDS Treatment Activists Coalition (ATAC), have won some victories at the state level and consistently pressure the federal government to fully fund ADAP. "The ADAP crisis has rallied one of the most energized grassroots efforts in a long time," says Ryan Clary of Save ADAP and Project Inform. "Anyone who is troubled by waiting lists for lifesaving drugs can and must do something about it, from calling and writing their elected representatives to joining SAVE ADAP and being part of a national movement to increase ADAP funding."

For the latest information on the ADAP crisis, see NASTAD's ADAP Funding Watch, posted online every two months at http://www.nastad.org, or visit the Title II Community AIDS National Network (TII CANN) website at http://www.tiicann.org.

Join Save ADAP by visiting http://www.atac-usa.org and clicking on Save ADAP, or contact Ryan Clary at rclary@projectinform.org or 415.558.8669x224.

Medicaid: Out-of-Pocket Expenses and Access to Care

by Suzy Subways

Over the past few years, several states have increased or begun charging out-of-pocket expenses for Medicaid, State Children's Health Insurance Program (SCHIP), and other public health programs that help many Americans without private health insurance pay for medical care and treatment. On May 27, the Kaiser Family Foundation's Commission on Medicaid and the Uninsured released "Increasing Premiums and Cost Sharing in Medicaid and SCHIP: Recent State Experiences," a report on how increased premiums and cost-sharing affect the ability of people with low incomes to keep their Medicaid and SCHIP coverage.

Kaiser's Samantha Artiga and Molly O'Malley examined 13 studies done in seven states from 2001 to 2005. Oregon provided a striking example of lost access to care: In 2003, the state increased Medicaid premiums for poor adults to between $6 and $20 and eliminated waivers for the homeless. Enrollment dropped by roughly 50,000 people -- almost half of those on Medicaid. Sixty-seven percent of those dropped from the rolls became uninsured after that, and Oregon recorded an increase in emergency-room use by uninsured patients, as well as increased pressure on clinics.

The 27-page report can be found online at http://www.kff.org/medicaid/7322.cfm or by requesting publication number 7322 from the Kaiser Commission on Medicaid and the Uninsured at 202.347.5270 or 1330 G Street, NW, Washington, DC 20005.

Lexiva: Blood Levels Not Lowered When Taken Simultaneously with

Nexium

by John S. James

On April 29, 2005 GlaxoSmithKline announced that a drug-interaction trial of Lexiva (fosamprenavir) with Nexium (esomeprazole, a proton-pump inhibitor, often used to reduce stomach acidity for relief of reflux, the unwanted flow of stomach acid into the esophagus), had found no reduction in the in the blood level of amprenavir. The data were presented at the 6th International Workshop on Clinical Pharmacology of HIV Therapy, in Quebec [1].

The FDA-approved "label" for Lexiva (the official prescribing information for physicians) urges caution in using the drug together with proton-pump inhibitors, because experience with other drugs suggested that the blood level of the antiviral might be decreased, making it less effective (no test with Lexiva and Nexium had been done). But the company's randomized crossover trial in 48 HIV-negative volunteers who took Lexiva for two weeks with Nexium, and later for two weeks without, found that this did not happen, at least with the 20 mg dose of Nexium tested (the drug is supplied in 20 and 40 mg doses) -- whether or not the Lexiva was "boosted" with a small dose of Norvir.

There was speculation that the timing of the doses might be important -- that because they were taken simultaneously in this study, the Lexiva might be absorbed before the Nexium had time to reduce stomach acidity. A previous study had shown a 30% reduction in blood concentration of amprenavir when Zantac (another drug for reducing stomach acidity) was given one hour before Lexiva [2].

Currently (June 2005) the official prescribing information is still the December 2004 version. Glaxo is seeking FDA permission to change it, in view of the new data. Any version with a later date should reflect the FDA's evaluation of the new information.

The current prescribing information is at http://www.lexiva.com/hcp/prescribingInformation.html. Look for the date at the end of the file.

Note: At the same conference Glaxo presented a similar study showing that tenofovir (Viread) did not affect amprenavir levels when used with Lexiva. This is consistent with prior information.

Comment

We urgently need more drug-interaction trials to guide physicians and reduce guesswork when multiple medications are prescribed. Companies that try to save money by skipping these trials put at risk a far larger investment, if their major drugs cannot be used optimally. These trials could aim for simple rules (such as choice of acid-reducing drugs, and delays when necessary) to avoid problems with antiretrovirals or other critical drugs that require stomach acidity in order to be fully absorbed. And small drug-level tests should check that results developed with HIV-negative volunteers do work for HIV-positive patients.

References

1. Shelton MJ, Ford SL, Wire MB, and others. Coadministration of esomeprazole (ESO) with fosamprenavir (fAPV) has no impact on steady-state plasma amprenavir (APV) pharmacokinetics (APV10031). 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005, Quebec City, Quebec [Abstract 24].

2. See "Gastric pH Modifiers" section on the Medscape (you need to register first, but that is free), http://www.medscape.com/viewarticle/505545.

New Conference for Frontline Clinicians, September 15 - 18

A new conference for HIV healthcare professionals (physicians, nurses, NPs, PAs, psychologists, case managers, and others, organized by 10 agencies of the U.S. government, will take place September 15 - 18 at the Hyatt Regency Atlanta, in Atlanta, Georgia. Highlighted topics include initial treatment for HIV, treatment strategies for late HIV,

comprehensive care and management, prevention, and associated infections and malignancies. The registration fee has been kept low: $250 general registration for the four-day meeting, $175 student or trainee (including the cost for continuing medical education credit).

The program committee is co-chaired by Paul Volberding, M.D., of the Center for AIDS Research at the University of California San Francisco, and Victoria Cargill, M.D. of the Office of AIDS Research (OAR) at the U.S. Department of Health and Human Services -- and includes 30 other experts. The steering committee is co-chaired by Lawrence Deyton, M.D., of the U.S. Department of Veterans Affairs, along with doctors Cargill and Volberding. John Bartlett, M.D., of Johns Hopkins University will give the keynote talk.

For more information visit the official conference Web site, http://www.USHIVconference.org.

Medical Innovation Prize Fund: New Idea in Drug Development

by John S. James

A proposal to change the way pharmaceuticals are developed by "separating the market for innovation from the market for medicines" has been introduced in Congress this year -- HR 417, by Rep. Bernard (Bernie) Sanders, Independent, Vermont. Under this plan, new drugs would be sold at generic prices as soon as the FDA approved them, and innovation would be rewarded not by high monopoly prices, but by a $60 billion per year fund, which would provide money to developers of new products based upon the actual impact on health outcomes over ten years.

Notably, this bill would not end pharmaceutical patents; in fact it would use them to distribute the prize fund. Companies would use patents as they do today to block competitors from registering products, but only until FDA marketing approval. Only patent owners could benefit from the Prize Fund payments.

HR 417 does not call for government price controls. Prices would be set by competition among generic manufacturers, which would be permitted as soon as a new drug is approved by the FDA. Generic suppliers will not be eligible for the prize money unless they had patents to show that they contributed to the innovation.

And government would not try to select in advance what research is promising. Investors would do that, betting their own money, as they do today. Government would have to control the prize awards, because billions of dollars of public money would be spent. But when the payment decisions were made, the results would be in; lives would already have been saved, and the award decisions could use standard data and estimates like QALYs (quality-adjusted life-years) to guide its decisions. The big difference is that investors would aim for improving public health, not for maximizing sales in a perverse market where the slightest advance in treating baldness or erectile dysfunction can pay more than a major advance in treating tuberculosis or malaria.

The legislation currently drafted would pay into the Medical Innovation Prize Fund at a level of 0.5% of the U.S. gross domestic product, or about $60 billion per year. The cost of pharmaceuticals in the U.S. today is close to $250 billion per year.

According to supporters of the Fund, out of the current US expenditures of $250 billion, only about $33 billion is reinvested in research and development (about 13%). About $25 billion of this is to develop new products, but only about $5 billion is invested in products that the FDA considers significantly better than existing drugs. (These figures do not include investment in research and development from non-U.S. sales.) Current U.S. royalties to pharmaceutical patent holders total about $10 to $12 billion. The bill's supporters believe that implementation of the Prize Fund would lead to much lower prices for medicines in the US (a decrease in prices of

$160 to $200 billion per year), while also increasing rewards for products that are innovative. The 0.5% of GDP level for the Prize Fund is the initial starting point, and subject to further debate.

The first public meeting to discuss HR 417 -- The Medical Innovation Prize Fund Act -- took place in Washington DC on June 17, 2005. For more information on this and other meetings contact Joy Spencer of the Consumer Project on Technology, joy.spencer@cptech.org.

For more information see
http://www.cptech.org/ip/health/hr417/
This page currently includes links to HR 417, a summary from Rep. Sanders' office, a sign-on letter, and background articles by specialists, including economists and attorneys.

Medical Innovation and Patent Gridlock

by John S. James

Today's pharmaceutical research and development has two huge problems, one widely recognized and the other often missed.

(1) New-Drug Prices

Under the current system most of the world's people will have no access to new, patented drugs for up to 20 years. For example, India recently changed its pharmaceutical patent laws as required by the World Trade Organization -- and (at least initially) omitted steps the WTO allows to make treatments more available. Multinational and Indian corporations are clearly aiming to sell new drugs to the richest 5% to 10%, meaning that 90% of the entire population of India will be denied access. Around the world, a substantial majority of all human beings may be disqualified from new drugs by patents and the resulting monopoly pricing. Financial inequality is so great that companies can make more money by selling to a small elite at prices that only it can pay, than by selling to everybody.

A June 1, 2005 report in a major AIDS journal (*JAIDS*) from a study of 306 patients in India found that of those treated over a year with one of two 3-drug regimens available, 46% had lipodystrophy [1]. The researchers also found that lipoatrophy was significantly associated with d4T use, and called for "improving access to alternative less-offending drugs like tenofovir and abacavir." This article ominously documents the development of a new global system of second-class medical care, imposed by trade laws that countries throughout the world have been pressured to accept.

But the biggest train wreck may involve cancer, not AIDS. Increasingly there will be highly targeted, very effective drugs against specific cancers (although resistance does develop); most of them will be patented, priced at tens of thousands of dollars a year in the U.S. (and likely close to that in poor countries), and often needed by each patient indefinitely. Reportedly one cancer drug already had a price increase about ten times in India, after courts stopped a generic company from selling the less expensive version.

Medical care for the poor has always been a disaster. But in the past the main problem was lack of enough resources to go around. The modern problem is the worldwide imposition of a system designed to sell new treatments at artificially high monopoly prices that most people cannot pay. In the U.S. many prescriptions are unfilled among the 45,000,000 uninsured. And those who are insured may be unable to afford copays, or denied treatment to save money.

(2) Patent Gridlock

Patent restrictions can block or greatly slow research and development of better treatments -- threatening the lives and health of everyone, even the richest, as no amount of money can quickly buy treatments and data that have never been created.

Patents do help innovation by providing incentives for investors to fund research and development (this necessary funding could be provided in other ways; for example, see "Medical Innovation Prize Fund: New Idea in Drug Development," above). But patents also block innovation. A patent means that only one company in the world can develop an idea (absent corporate dealmaking, a very